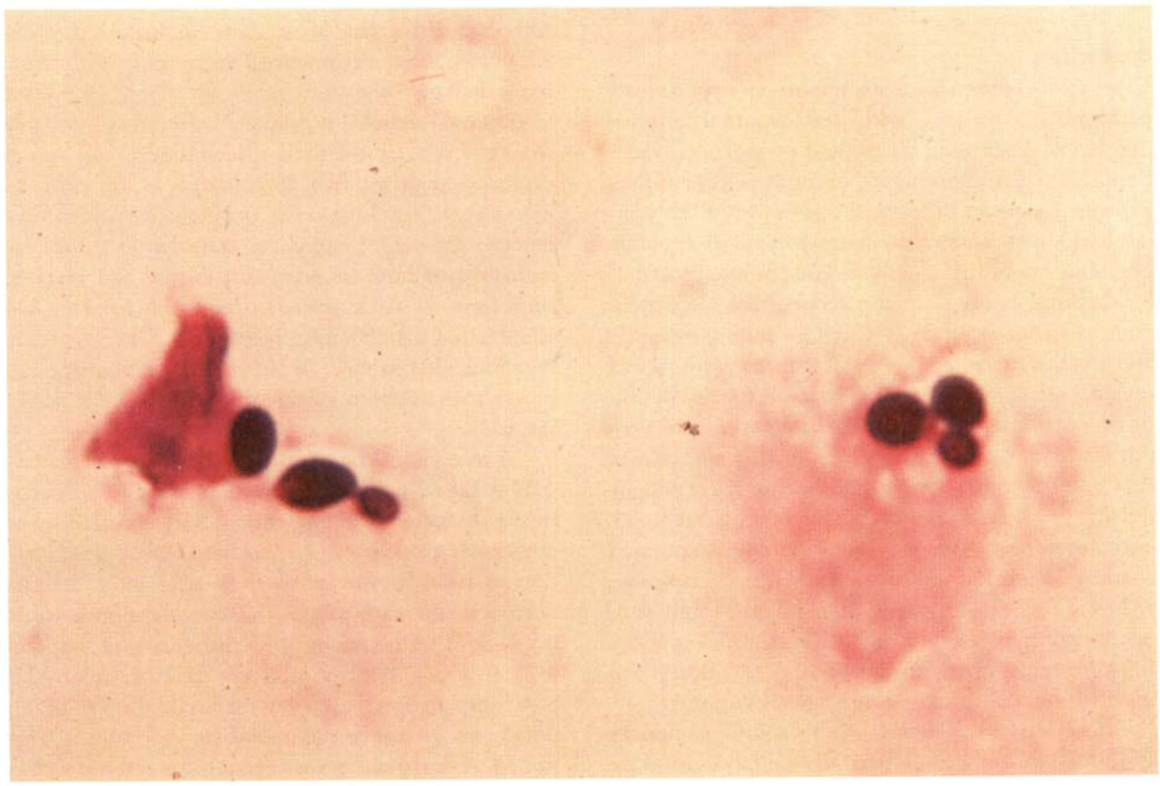
Illustrated continuing medical education



A 29-year-old Ugandan woman presented with a 4-week history of fever and headache. She had felt nauseous at times but had not vomited. Her husband had observed that over the previous week she had become much more lethargic and forgetful. She was not complaining of photophobia or neck stiffness, but had had some problems with blurred vision. She had arrived in the UK 4 months ago, as her 8-month-old child was unwell and had not been responding to treatment in her home country. He had since been diagnosed as being HIV positive

On examination she was thin and her temperature was 38.1°C. She was fully orientated and examination of her mental state was normal. There was no nuchal rigidity and Kernig's sign was negative. There were no focal abnormalities on examination of the nervous system. Investigations included a normal CT scan of the head and the following cerebrospinal fluid results; protein 0.61 g/L, glucose 2.2 mmol/L, white cells 98/mL (90% lymphocytes; 5% neutrophils; 5% degenerate), red cells 360/mL, Gram stain—see above.

Questions

1. Describe the Gram stain of the cerebrospinal fluid.
2. What is the likely cause of her presenting illness?
3. What is the best test to rapidly confirm this?
4. Five days after commencing treatment, her condition deteriorated. Over a 24-h period she became more confused and drowsy, and eventually lost consciousness. On examination she was afebrile, but was noted to have a left VIth nerve palsy. What complication had arisen?

Answers

1. The Gram stain shows Gram-positive, yeast-like organisms.
2. Meningitis due to *Cryptococcus neoformans* (secondary to HIV infection).
3. Testing of blood or cerebrospinal fluid for cryptococcal antigen.
4. She has developed raised intracranial pressure (the VIth nerve palsy is a false localizing sign).

Discussion

Cryptococcus neoformans is an important opportunistic pathogen in patients with the acquired immune deficiency syndrome (AIDS), and cryptococcal infections, particularly meningitis, occur in 5–10% of these patients. Based on differential expression of the polysaccharide capsular antigen, four serotypes (A–D) of the organism can be distinguished. Two varieties, based on biochemical testing, are also recognized; *Cryptococcus neoformans* var. *neoformans* (which includes serotypes A and D) and *Cryptococcus neoformans* var. *gatti* (which includes serotypes B and C). The vast majority of cases of cryptococcal meningitis associated with AIDS are due to *Cryptococcus neoformans* var. *neoformans* serotype A. Central nervous system infection in these patients usually presents as a subacute meningitis/meningoencephalitis with lethargy, fever, headache, personality changes, confusion and memory loss occurring over a 2–4-week period. Signs of meningism and focal neurologic signs are present in less than 5% of cases. In AIDS patients, involvement of a secondary site, usually lung, skin or blood, is relatively common.

Infection in patients with AIDS is usually associated with high numbers of organisms and these may be seen on Gram staining of the cerebrospinal fluid (CSF). However, the conventional method of visualization is by India ink staining of CSF, which will demonstrate the encapsulated organism in ~50% cases. The most sensitive and specific rapid diagnostic test is the detection of cryptococcal polysaccharide capsular antigen in CSF or blood, and this test is positive in 90–95% of cases. The definitive diagnosis is made by culture, and in primary cryptococcal meningitis the organism can normally be grown from the CSF.

Although not proved by large comparative trials, it is generally recommended that the initial treatment of cryptococcal meningitis should be with amphotericin B with or without flucytosine. As patients with AIDS often require prolonged treatment, early therapy with amphotericin B (which gives rapid clearance of the organism) is often followed by a triazole such as fluconazole or itraconazole. Such regimens have been successful in reducing mortality in this patient group. Although there has been some success in treating AIDS-associated cryptococcal meningitis with azole monotherapy, response rates are only 50–60%. *Cryptococcal meningitis* in patients with AIDS inevitably relapses once treatment is discontinued, and recent evidence suggests that fluconazole is superior to itraconazole for long-term maintenance suppressive therapy. Although prophylactic triazoles do reduce the incidence of both cryptococcal disease and mucosal candidiasis in AIDS patients (especially if the CD4 count is less than 50/mL), prophylaxis is not generally recommended in view of lack of survival benefit and the risk of selection of fluconazole-resistant *Candida* species.

A recognized complication of cryptococcal meningitis is raised intracranial pressure, which can occur in the absence of cerebral edema. Sudden increases of intracranial pressure can lead to rapid clinical deterioration and death, and as the CT scan often appears normal in the early stages, this complication is easily overlooked. The majority of patients will respond to therapeutic lumbar puncture and, although this procedure may need to be repeated, the condition usually resolves once the underlying infection is controlled. A few patients may require the insertion of a temporary ventricular shunt or lumbar drain. Although corticosteroids and acetazolamide (which reduces the production of CSF) have been used in the management of patients with raised intracranial pressure, the use of these agents is not routinely recommended.

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Clinical Microbiology and Infection would welcome similar Illustrated Continuing Education pieces to be submitted to the Editorial Office. Photographs may be clinical pictures, plates, films, radiographs, or indeed anything which is of relevance to the clinical case. Please see Instructions to Authors for manuscript style and also include three colour/black-and-white photographs of at least 10×8 inches. A letter surrendering copyright of the photographs to ESCMID should accompany the case, and a letter of consent will also be required if identification of a patient is possible from the photograph.

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